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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/635,108	08/05/2003	Stephen Scaringe	13561	6956

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EXAMINER	
SISSON, BRADLEY L	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 06/22/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/635,108	SCARINGE, STEPHEN	
	Examiner	Art Unit	
	Bradley L. Sisson	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 April 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9 and 11-24* is/are pending in the application.

4a) Of the above claim(s) *24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9 and 11-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/27/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 27 April 2005 has been entered.

Election/Restrictions

2. Newly submitted claim 24 is directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: The method results in the determination of whether or not a given gene product is a suitable target for drug discovery. This is distinct fro the method of claims 9 and 11-23 as there the claimed method results in the inhibition of mRNA.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claim 24 has been withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Specification

3. The disclosure is objected to because of the following informalities: A review of the record locates Figures 1A-1D, and Figure 2 through Figure 7, yet page 12 of the disclosure makes reference to a Fig. Y. Said Fig. Y has not been located in the instant application.

Appropriate correction is required.

4. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 9 and 11-23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Attention is directed to the decision in *University of Rochester v. G.D. Searle & Co.* 68 USPQ2D 1424 (Fed. Cir. 2004) at 1428:

> To satisfy the written-description requirement, the specification must describe every element of the claimed invention in sufficient detail so that one of ordinary skill in the art would recognize that the inventor possessed the claimed invention at the time of filing. Vas-Cath, 935 F.3d at 1563; see also Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572 [41 USPQ2d 1961] (Fed. Cir. 1997) (patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention"); In re Gosteli, 872 F.2d 1008, 1012 [10 USPQ2d 1614] (Fed. Cir. 1989) ("the description must clearly allow persons of

ordinary skill in the art to recognize that [the inventor] invented what is claimed"). Thus, an applicant complies with the written-description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572.

For convenience, claims 9 and 11 are reproduced below.

9. (currently amended) A method for inhibiting an mRNA, comprising:

a) providing an RNA comprising the structure X_1-L-X_2, wherein X_1 and X_2 are nucleotide sequences having sufficient complementarity to one another to form a double-stranded stem hybrid and L is a flexible loop region comprising a non-nucleotide linker molecule of 10-24 atoms in length, wherein at least a portion of one of the nucleotide sequences located within the double-stranded stem is complementary to a sequence of the target mRNA; and

b) contacting the RNA comprising the structure X_1-L-X_2 with a sample *in vitro* containing or suspected of containing the target mRNA under conditions that favor transfection of the RNA comprising the structure X_1-L-X_2 into a cell comprising the target mRNA whereby presence of the RNA comprising the structure X_1-L-X_2 decreases expression of the target mRNA;

wherein X_1 and X_2 each independently comprise between about 19 to 27 nucleotides, and L comprises a polyether, a polyamine, a polyester, a polyphosphodiester, an alkylene, or a combination thereof.

11. (previously presented) The method according to claim 9, wherein L is a polyether and the polyether comprises a polyethylene glycol, a polyalcohol, a propylene glycol, or a combination thereof.

7. For purposes of examination, the claimed method has been interpreted and encompassing inhibition of mRNA expression in any and all manner of life forms, be it plant, animal, or single-cell organism. A review of the disclosure fails to locate an adequate written description of the starting materials and the conditions under which they are to be made and used in accordance with the claimed method. Acknowledgement is made that the specification seeks to incorporate by reference pertinent disclosures of US Patents 5,889,136 and 6,111,086. The cited documents,

however, have not been found to each the manufacture of the requisite starting materials, e.g., RNA comprising the structure X1-L-X2, wherein L is "a polyether, a polyamine, a polyester, a phosphodiester, an alkylene, or a combination thereof," wherein the polyether "comprises a polyethylene glycol, a polyalcohol, a propylene glycol or a combination thereof." While the instant disclosure states at page 12, line 22, that the "oligonucleotide synthesis were adapted from" these patents, the instant disclosure also fails to provide a full, clear, and concise description of the requisite starting materials, or of the manner in which prior art methodologies must be modified so as to yield the requisite starting material.

8. In accordance with claims 16-19, the RNA structure is to comprise a left hairpin, a right hairpin, or a bulge, which can be a "stem loop bulge." A review of the disclosure fails to locate an adequate written description of these requisite starting materials, much less a description of the amount of complementarity needed between the RNA to be transfected, which has these secondary structures, and the target mRNA in the cell such that a decrease in expression is observed.

9. A review of the disclosure finds the following examples:

a. Example 1, "Hairpin Design," pages 11-14; and

b. Example 2, "Hairpin Design with different overhangs," pages 14-15."

10. None of the examples are drawn to the claimed methods. A review of the disclosure fails to find an adequate written description of how the two methods are to be practiced. With the claims encompassing performing the method *in* vitro, the manner and means of introducing RNA having the structure X_1-L-X_2 into any cell and have such transfection result in the desired end product is most difficult and unpredictable.

11. For the above reasons, the application as filed does not provide such a full, clear, and concise description of the invention so as to reasonably suggest that applicant had possession of the full genus of the method at the time of filing. It appears that applicant is attempting to satisfy the written description requirement of 35 USC 112, first paragraph, through obviousness. Obviousness, however, cannot be relied upon for satisfaction of the written description requirement. In support of this position, attention is directed to the decision in *University of California v. Eli Lilly and Co.* (Fed. Cir. 1997) 43 USPQ2d at 1405, citing *Lockwood v. American Airlines Inc.* (Fed. Cir. 1997) 41 USPQ2d at 1966:

> Recently, we held that a description which renders obvious a claimed invention is not sufficient to satisfy the written description requirement of that invention.

For the above reasons, and in the absence of convince evidence to the contrary, claims 9 and 11-23 9 and 11-23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

Response to argument

12. At pages 5-8 of the response received 27 April 2005, applicant's representative presents argument as to what one of skill in the art would have been able to understand. Said representative provides at pages 6-7 of the response a synopsis of various non-patent publications. Such showings, however, do not take the place of sworn (declarations/affidavits) evidence and from which assurances that any statements or representations made are correct, as provided by 35 U.S.C. 25 and 18 USC 1001. *Ex parte Gray* 10 USPQ2d 1922 at 1928 (BPAI 1989). Accordingly, applicant's representative's argument is non-persuasive.

13. Claims 9 and 11-23 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. As set forth in *Enzo Biochem Inc., v. Calgene, Inc.* (CAFC, 1999) 52 USPQ2d at 1135, bridging to 1136:

> To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.' " *Genentech, Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997) (quoting *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)). Whether claims are sufficiently enabled by a disclosure in a specification is determined as of the date that the patent application was first filed, see *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986).... We have held that a patent specification complies with the statute even if a "reasonable" amount of routine experimentation is required in order to practice a claimed invention, but that such experimentation must not be "undue." See, *e.g.*, *Wands*, 858 F.2d at 736-37, 8 USPQ2d at 1404 ("Enablement is not precluded by the necessity for some experimentation . . . However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' ") (footnotes, citations, and internal quotation marks omitted). In *In re Wands*, we set forth a number of factors which a court may consider in determining whether a disclosure would require undue experimentation. These factors were set forth as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *Id.* at 737, 8 USPQ2d at 1404. We have also noted that all of the factors need not be reviewed when determining whether a disclosure is enabling. See *Amgen, Inc. v. Chugai Pharm. Co., Ltd.*, 927 F.2d 1200, 1213, 18 USPQ2d 1016, 1027 (Fed. Cir. 1991) (noting that the *Wands* factors "are illustrative, not mandatory. What is relevant depends on the facts.").

14. The specification teaches that the claimed method is to employ short interfering hairpin RNA in a variety of methods, including the treatment of any "plant, animal or human suspected of having or being prone to a disease or condition associated with expression of a target gene" (page 4 second paragraph, of the specification). Said methods of inhibiting mRNA (claims 9 and

11-23) have also been interpreted as fairly encompassing the "knocking down (partially or completely) a targeted gene, for example for generating models of disease states, to examine the function of a gene, to assess whether an agent acts on a gene, to validate targets for drug discovery, etc." (Specification at page 10, fist paragraph).

15. Clearly, the claimed method requires the transfection of cells with RNA that will hybridize to the target mRNA (an antisense RNA) and that this transfected RNA is to hybridize to the target with such specificity that there is observed a decrease in expression of the encoded protein. This area of art is recognized as being quite problematic. In support of this position, attention is directed to paragraph 105 of US 2004/0157771 A1, which has been reproduced below in pertinent part:

> A number of methods have been developed for delivering antisense DNA or RNA to cells; e.g., antisense molecules can be injected directly into the tissue or cell derivation site, or modified antisense molecules, designed to target the desired cells (e.g., antisense linked to peptides or antibodies that specifically bind receptors or antigens expressed on the target cell surface) can be administered systemically. However, *it is often difficult to achieve intracellular concentrations of the antisense sufficient to suppress translation of endogenous mRNAs.* (Emphasis added)

16. The instant disclosure is essentially silent as to how the virtually limitless combinations of components X1, X2, and L) are each transfected into any cell in a manner such that an actual decrease in mRNA expression.

17. A review of the disclosure fails to find where any one, much less all of the intended utilities have been fully enabled by the specification, regardless of whether they are to be gene therapy, or the identification of a gene as a suitable target for drug development.

18. The specification fails to set forth the requisite starting materials and reaction conditions that would permit one of skill in the art at the time the invention was made to reproducibly

manufacture any and all useful interfering hairpin RNA molecules. While the specification makes reference to various documents, the disclosure does not provide the requisite starting materials and reaction conditions. The specification is silent as to what drugs (mRNA sequences) are to be used, and how these sequences are to be introduced into any population of target cells, much less be caused to selectively diminish mRNA transcription without resulting in toxicity to the cell(s) (specification at page 16). The situation at hand is analogous to that in *Genentech v. Novo Nordisk A/S* 42 USPQ2d 1001. As set forth in the decision of the Court:

> " '[T]o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation.' *In re Wright* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *see also Amgen Inc. v. Chugai Pharms. Co.*, 927 F. 2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed Cir. 1991); *In re Fisher*, 427 F. 2d 833, 166 USPQ 18, 24 (CCPA 1970) ('[T]he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art.').
>
> *****
>
> "Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. *See Brenner v. Manson*, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (starting, in context of the utility requirement, that 'a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.') Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention. "It is true . . . that a specification need not disclose what is well known in the art. *See, e.g., Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. <u>However, when there is no disclosure of any specific starting material or any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art.</u> It is the

> specification, not the knowledge of one skill in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. This specification provides only a starting point, a direction for further research. (Emphasis added)

19. With no specific starting material or reaction conditions provided, the skilled artisan would have to resort to trial and error experimentation with little if any reasonable expectation of success. Such level of effort required to the exerted by the skilled artisan is undue. Therefore, and in the absence of convincing evidence to the contrary, claims 9-23 are rejected under 35 USC 112, first paragraph, as failing to comply with the enablement requirement.

Response to argument

20. At page 8, bridging to page 10 of the response said representative asserts that as a result of the amendment to the claims to exclude *in vivo* treatment, and the preceding remarks regarding the written description-based rejection, the enablement-based rejection of claims under 35 USC 112, first paragraph, should be withdrawn.

21. While the claims have been amended so to avoid the issue of enablement as it relates to *in vivo* treatment, the claimed method is still rejected. As noted above, the written description rejection is maintained, as the specification does not reasonably suggest that applicant had possession of the invention at the time of filing. In view of one not being able to enable that which they o not yet possess, and in view of the specification not providing the essential starting materials, reaction conditions, and guidance as to how to overcome art-recognized difficulties, claims 9 and 11-23 remain rejected under 35 USC 112, first paragraph, as failing to comply with the enablement requirement.

Conclusion

22. All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

23. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

24. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bradley L. Sisson whose telephone number is (571) 272-0751. The examiner can normally be reached on 6:30 a.m. to 5 p.m., Monday through Thursday.

25. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached on (571) 272-0745. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

26. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

B. L. Sisson

Bradley L. Sisson
Primary Examiner
Art Unit 1634

BLS
20 June 2005